(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
WO 02/072069 A1

(51) International Patent Classification[7]: A61K 9/14, 9/20, 9/48

(21) International Application Number: PCT/DK02/00163

(22) International Filing Date: 12 March 2002 (12.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2001 00413 12 March 2001 (12.03.2001) DK

(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).

(72) Inventors: HJORTH, Thyge, Borup; Solbakken 5, DK-3520 Farum (DK). KNUDSEN, Breian; Porsager 55, DK-2620 Albertslund (DK).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/072069 A1

(54) Title: NOVEL TABLETS AND CAPSULES AND A PROCESS FOR ITS PREPARATION

(57) Abstract: Tablets and capsules wherein the content of active ingredient in the tablet or capsule is not more than about 3 % (weight/weight) can be prepared if microcrystalline cellulose and silicon dioxide are used as some of the starting materials.

Novel tablets and capsules and a process for its preparation.

FIELD OF THE INVENTION

The present invention relates to novel tablets and capsules with relatively low amounts of the active ingredient. The present invention further relates to tablets and capsules comprising as the active ingredient (-) 3-[4-[2-(phenoxazin-10-yl) ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt thereof.

BACKGROUND OF THE INVENTION

In US patent 5,948,438 and US patent 6,106,865 oral solid dosage forms comprising microcrystalline cellulose and a compressibility augmenting agent such as silicon dioxide are described.

(2S)(-)-3-[4-[2-(phenoxazin-10-yl) ethoxy]phenyl]-2-ethoxypropanoic acid (in the following (-) 3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid) and pharmaceutically acceptable salts thereof has been found useful in the treatment of type 2 diabetes acting as an insulin sensitizer as disclosed in eg PCT Publication WO 99/19313, WO 00/50414 and WO 00/63192, which are incorporated herein by reference. Pharmaceutical compositions containing (-) 3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid as active ingredient or a pharmaceutically acceptable salt thereof are described in WO01/74363.

One object of the present invention is to provide tablets and capsules having improved homogeneity.

Another object of the present invention is to provide tablets and capsules having improved homogeneity with respect to the content of active ingredient.

Another object of the present invention is to provide tablets and capsules having improved homogeneity with respect to the distribution of active ingredient.

Another object of the present invention is to provide tablets and capsules having a low content of active ingredient.

A still further object of the present invention is to provide tablets and capsules being superior to the known art.

SUMMARY OF THE INVENTION

It has now been found that a tablet or capsule wherein the content of active ingredient in the tablet or capsule is between about 3 % (weight/weight) and about 0.001 % (weight/weight) can be prepared with improved homogenous distribution of the active ingredient if microcrystalline cellulose and silicon dioxide are used as some of the starting materials. Surprisingly, it has now been found that a tablet or capsule wherein the content of active ingredient in the tablet or capsule is not more than about 2 % (weight/weight) can be prepared with improved homogenous distribution of the active ingredient if microcrystalline cellulose and silicon dioxide are used as some of the starting materials. Using these starting materials, it is even possible to prepare tablets and capsules wherein the content of active ingredient in the tablet or capsule is not more than about 1 %, not more than about 0.5 %, not more than about 0.05 %, not more than about 0.01 %, and even not more than about 0.005 % (weight/weight).

It is a further object of the present invention to provide a tablet or capsule with improved homogenous distribution which comprises microcrystalline cellulose and silicon dioxide and (-) 3-[4-[2-(phenoxazin-10-yl) ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt thereof.

MORE DETAILED DESCRIPTION OF THE PRESENT INVENTION

Generally, any sort of microcrystalline cellulose can be used for the preparation of the tablets and capsules according to the present invention. However, it is preferred that the microcrystalline cellulose used for the preparation of the tablets and capsules according to the present invention has a bulk density above 0.35 g/ml. Furthermore, it is preferred that the microcrystalline cellulose used for the preparation of the tablets and capsules according to the present invention has a particle size above about 50 micrometer. A tablet or capsule according to the present invention comprises preferably microcrystalline cellulose in an amount of at least 20 %, more preferred of at least 30 % and even more preferred of at least 40 % (weight/weight) and most preferred in an amount of at least 45% (weight/weight). For example, the tablet or capsule according to the invention comprises microcrystalline cellulose in amounts ranging from 20% to 80% (weight/weight) , amounts from 30% to 70% are preferred while amounts

from 40% to 60% are even more preferred and amounts ranging from 45% to 55% are especially preferred.

Similarly, any sort of silicone dioxide can be used for the preparation of the tablets and capsules according to the present invention. However, it is preferred that the silicone dioxide used for the preparation of the tablets and capsules according to the present invention has a particle size from about 1 namometer to about 100 micrometer. A tablet or capsule according to the present invention comprises preferably an amount of silicone dioxide in the range from 0.1 to 5 %, preferably in the range from 0.2% to 3%, even more preferred in the range from 0.5% to 1,5% (weight/weight).

In another embodiment according to the present invention, the tablet or capsule further comprises mannitol. In a preferred embodiment according to the invention, the tablet or capsule comprises mannitol in an amount of at least 20%, preferably at least 30% an even more preferred at lest 40% (weight/weight) and most preferred in an amount of at least 45% (weight/weight). In preferred embodiments of the invention, the tablet or capsule comprises mannitol in amounts ranging from 20% to 80% (weight/weight) , amounts from 30% to 70% are preferred while amounts from 40% to 60% are even more preferred and amounts ranging from 45% to 55% are especially preferred.

In another embodiment of the present invention, the tablet or capsule comprises mannitol and microcrystalline cellulose in proportions between 2:8 and 8:2, preferably between 3:5 and 5:3, more preferred between 4:6 and 6:4, and even more preferred between 45:55 and 55:45.

In another embodiment of the present invention, the tablet or capsule comprises talc in the range from 0.1 to 10 % (weight/weight).

In a further preferred embodiment of the invention, the tablet or capsule comprises microcrystalline cellulose in an amount ranging from 45% to 55% and silicon dioxide in an amount from 0,5% to 1,5%(weight/weight).

In another embodiment of the invention, the tablet or capsule comprises: (i) an active ingredient selected from the group consisting of (-) 3-[4-[2-(phenoxazin-10-yl) ethoxy]phenyl]-2-ethoxypropanoic acid, pharmaceutically acceptable salt, ester, metabolite, hydrate, solvate,

polymorph, and pro-drug form thereof, (ii) microcrystalline cellulose; and (iii) silicon dioxide, wherein the amount of said active ingredient is between about 0.01% and about 2,0% (weight/weight); the amount of said microcrystalline cellulose is between about 40% and about 50% (weight/weight); and the amount of said silicone dioxide is between about 0.8% and about 1.2% (weight/weight).

Non-limiting examples of a formulation according to invention include the following (expressed as % weight/ total weight of each ingredient):

Active ingredient	1%
Microcrystalline cellulose	97.8-98.2%
Silicon dioxide	0.8-1.2%

Active ingredient	1%
Microcrystalline cellulose	47%
Silicon dioxide	1%
Mannitol	47%
Talc	4%

Active ingredient	1%
Microcrystalline cellulose	45.2%
Silicon dioxide	0.8%
Mannitol	49%
Talc	4%

Active ingredient	0.5%
Microcrystalline cellulose	98.3-98.7%
Silicon dioxide	0.8-1.2%

Active ingredient	2%
Microcrystalline cellulose	96.8-97.2%
Silicon dioxide	0.8-1.2%

Active ingredient	0.2%

Microcrystalline cellulose	98.6-99.0%
Silicon dioxide	0.8-1.2

Active ingredient	2%
Microcrystalline cellulose	46.5%
Silicon dioxide	1%
Mannitol	46.5%
Talc	4

In a preferred embodiment of the present invention, the tablets or capsules are prepared using one of the commercial products marketed under the designations ProSolv HD 90, ProSolv SMCC 50, and ProSolv SMCC 90 by the firm PenWest, each of which contain both microcrystalline cellulose and silicon dioxide.

In one aspect of the present invention, the tablets or capsules have a relative standard deviation (RSD) for the content of active ingredient in the tablet or capsule which is not more than about 4%. Preferably, the RSD value is not more than about 3 %, more preferred the RSD value is not more than about 2,5 %, and even more preferred the RSD value is not more than about 2 %, especially preferred the RSD value is not more than about 1,5 %, and even more preferred the RSD value is not more than about 1 %.

The relative standard deviation (RSD) for the content of active ingredient in the tablets of the present invention can be determined as described in the United States Pharmacopeia (USP 24) 2000, chapter 905 using the test for Uniformity of Dosage Units, <905>, USP XV.

The bulk and tapped density can be determined as described in method BTD-8, Handbook of Pharmaceutical Excipients, 2nd ed., 1994. Particle size distribution can be determined by Sieve analysis using US standard sieves.

The tablets and capsules according to the present invention can be prepared in a manner known *per se*. More specifically, the tablets and capsules may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th edition, 1995. According to a preferred feature of the present invention, the tablet or capsule according to the present invention are prepared by direct compression. Direct compression has

the advantage that it is possible to first mix all the ingredients which are to be present in the final tablet or capsule and then to subject the mixture to direct compression.

The active ingredient present in the tablets and capsules of the present invention can be any pharmaceutical such as analgesics and anti-inflammatory agents, anthelminthics, anti-arrhythmic agents, antibacterial agents, anticoaglants, antidepressants, antidiabetic agents, antiepileptics, antifungal agents, antigout agents, antihypertensive agents, antimalarials, antimigraine gents, antimuscarinic agents, antineoplastic agents, immunosuppressants, antiprotozoal agents, antithyroid agents, antiviral agents, anxiolytic sedatives, hypnotics, neuroleptics, beta-adrenoceptor blocking agents, calcium regulating agents, cardiac inotropic agents, chelating agents, antidotes, antagonists, corticosteroids, diuretics, dopaminergic antiparkinsonian agents, gastro-intestinal agents, anaesthetics, hormones, lipid regulating agents, , anti-angina agents, vitamins, anti-asthma agents, skeletal muscle relaxants, stimulants, anoretics, sympatomimetics, thrombolytic agents, and vasodilators.

An example of a specific medicaments is (-) 3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid and pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts forming part of this invention include salts such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminium salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulplionates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference.

The present invention also encompasses esters, metabolites, hydrates, solvates, polymorphs, and pro-drug forms of (-) 3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid.

In a preferred embodiment, (-) 3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine is used in the present invention.

Another example of a specific medicament is 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof as active ingredient as described in PCT Publication WO 97/41097. The present invention also encompasses esters, metabolites, hydrates, solvates, polymorphs, and pro-drug forms of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione.

Examples of suitable carriers present in the tablets and capsules according to the present invention are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, mannitol, sorbitol, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The tablets and capsules may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The tablets and capsules of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The tablets and capsules can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch.

The tablets and capsules of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of

various diseases as mentioned above. Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The exact dosage of the tablets and capsules will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The present invention will further be illustrated with the following non-exhaustive examples.

EXAMPLE 1

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	3.860g
Microcrystalline cellulose with 2% silicon dioxide	1423g
Mannitol	1423g
Magnesium stearate	30g
Talc	120g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide is mixed in a drum mixer for 5 minutes. Mannitol and the rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

The results from test for content uniformity according to USP gave the following results:

Mean content of (-) 3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid in each tablet:

0.0973mg

RSD: 1.17%

EXAMPLE 2

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	3.860g

Microcrystalline cellulose with 2% silicon dioxide	2846g
Magnesium stearate	30g
Talc	120g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide is mixed in a drum mixer for 5 minutes. The rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

The results from test for content uniformity according to USP gave the following results:

Mean content of (-) 3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid in each tablet:

0.103mg

RSD: 1.85%

EXAMPLE 3

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	3.860g
Microcrystalline cellulose with 2% silicon dioxide	1708 g
Mannitol	1138 g
Magnesium stearate	30g
Talc	120 g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide is mixed in a drum mixer for 5 minutes. Mannitol and the rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

EXAMPLE 4

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	3.860g
Microcrystalline cellulose with 2% silicon dioxide	1138 g
Mannitol	1708 g
Magnesium stearate	30g
Talc	120 g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide is mixed in a drum mixer for 5 minutes. Mannitol and the rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

EXAMPLE 5

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	3.860g
Microcrystalline cellulose with 2% silicon dioxide	1897 g
Mannitol	949 g
Magnesium stearate	30g
Talc	120 g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide ismixed in a drum mixer for 5 minutes. Mannitol and the rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

EXAMPLE 6

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	3.860g
Microcrystalline cellulose with 2% silicon dioxide	949 g
Mannitol	1897 g
Magnesium stearate	30g
Talc	120 g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide is mixed in a drum mixer for 5 minutes. Mannitol and the rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

EXAMPLE 7

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	3.860g
Microcrystalline cellulose with 2% silicon dioxide	407 g
Mannitol	2439 g
Magnesium stearate	30g
Talc	120 g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide is mixed in a drum mixer for 5 minutes. Mannitol and the rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

EXAMPLE 8

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	3.860g
Microcrystalline cellulose with 2% silicon dioxide	2439 g
Mannitol	407 g
Magnesium stearate	30g
Talc	120 g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide is mixed in a drum mixer for 5 minutes. Mannitol and the rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

EXAMPLE 9

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	3.860g
Microcrystalline cellulose	90 g
Lactose, monohydrate	2885
Silica, colloidal anhydrous	6 g
Magnesium stearate	15 g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 90 g of microcrystalline cellulose is mixed in a drum mixer for 5 minutes. Lactose and silica is added and mixing is continued for 10 minutes. Magnesium stearate is added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

EXAMPLE 10

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	19.30g
Microcrystalline cellulose with 2% silicon dioxide	1693 g
Mannitol	1138 g
Magnesium stearate	30g
Talc	120 g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide is mixed in a drum mixer for 5 minutes. Mannitol and the rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture are compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

EXAMPLE 11

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt	1.930g
Microcrystalline cellulose with 2% silicon dioxide	950 g
Mannitol	1898 g
Magnesium stearate	30g
Talc	120 g

Manufacture:

(-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt, and 200g of microcrystalline cellulose with silicon dioxide is mixed in a drum mixer for 5 minutes. Mannitol and the rest of microcrystalline cellulose with silicon dioxide is added and mixing is continued for 10 minutes. Magnesium stearate and talc are added and mixed for further 5 minutes.

The powder mixture is compressed into tablets on a tabletting machine. The tablet weight is 110 mg.

CLAIMS

1. A tablet or capsule containing microcrystalline cellulose and silicon dioxide and active ingredient in an amount between about 3 % and about 0.001 % (weight/ weight).

2. A tablet or capsule, according to claim 1, wherein the content of active ingredient is not more than about 2 % (weight/weight).

3. A tablet or capsule, according to claim 1, wherein the content of active ingredient is not more than about 1 %(weight/weight).

4. A tablet or capsule, according to any one of the preceding claims, wherein the content of active ingredient is not more than about 0.5 %(weight/weight).

5. A tablet or capsule, according to any one of the preceding claims, wherein the content of active ingredient is not more than about 0.05 %(weight/weight).

6. A tablet or capsule, according to any one of the preceding claims, wherein the content of active ingredient is not more than about 0.01 % (weight/weight).

7. A tablet or capsule, according to any one of the preceding claims, wherein the content of active ingredient is not more than about 0.005 %(weight/weight).

8. A tablet or capsule, according to any one of the preceding claims, wherein the active ingredient is (-) 3-[4-[2-(phenoxazin-10-yl) ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt thereof.

9. A tablet or capsule, according to any one of the preceding claims, wherein the active ingredient is (-) 3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid, arginine salt

10. A tablet or capsule, according to any one of the preceding claims, which further comprises mannitol.

11. A tablet or capsule according to any one of the preceding claims comprising mannitol and microcrystalline cellulose in proportions between 2:8 and 8:2, preferably between 3:5 an 5:3, even more preferred between 4:6 and 6:4, and most preferred between 45:55 and 55:45.

12. A tablet or capsule according to any one of the preceding claims comprising silicon dioxide in the range from 0.1 to 5 %, preferably in the range from 0.2% to 3%, and even more preferred in the range from 0.5% to 1,5% (weight/weight).

13. A tablet or capsule according to any one of the preceding claims comprising microcrystalline cellulose in an amount ranging from 45% to 55% and silicon dioxid in an amount ranging from 0,5% to 1,5% (weight/weight).

14. A tablet or capsule, according to any one of the preceding claims, wherein the microcrystalline cellulose has a bulk density above 0.35 g/ml.

15. A tablet or capsule according to any one of the preceding claims, wherein the microcrystalline cellulose has a particle size above about 50 micrometer.

16. A tablet or capsule according to any one of the preceding claims, wherein the silicone dioxide has a particle size from about 1 namometer to about 100 micrometer.

17. A tablet or capsule according to any one of the preceding claims containing ProSolv HD 90, ProSolv SMCC 50, and ProSolv SMCC 90 (from PenWest).

18. A tablet or capsule according to any one of the preceding claims for which the relative standard deviation (RSD) for the content of active ingredient in the tablet or capsule is not more than about 4%.

19. A tablet or capsule according to any one of the preceding claim for which the RSD value is not more than about 3 %.

20. A tablet or capsule according to any one of the preceding claims for which the RSD value is not more than about 2,5 %.

21. A tablet or capsule according to any one of the preceding claims for which the RSD value is not more than about 2 %.

22. A tablet or capsule according to any one of the preceding claims for which the RSD value is not more than about 1,5 %.

23. A tablet or capsule according to any one of the preceding claims for which the RSD value is not more than about 1 %.

24. A process for preparing a tablet or capsule according to any one of the preceding claims which process is characterized in that the tablets or capsules are prepared by direct compression.

25. A tablet or capsule which comprises microcrystalline cellulose and silicon dioxide and wherein the active ingredient is (-) 3-[4-[2-(phenoxazin-10-yl) ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt thereof.

26. A tablet or capsule comprising: (i) an active ingredient selected from the group consisting of (-) 3-[4-[2-(phenoxazin-10-yl) ethoxy]phenyl]-2-ethoxypropanoic acid, pharmaceutically acceptable salt, ester, metabolite, hydrate, solvate, polymorph, and pro-drug form thereof.; (ii) microcrystalline cellulose; and (iii) silicon dioxide, wherein the amount of said active ingredient is between about 0.01% and about 2,0% (weight/weight); the amount of said microcrystalline cellulose is between about 40% and about 50% (weight/weight); and the amount of said silicone dioxide is between about 0.8% and about 1.2% (weight/weight).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00163

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K9/20 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 30016 A (JANSSEN PHARMACEUTICA NV) 3 October 1996 (1996-10-03) claim 8; example 1 ---	1-7
X	GB 2 055 575 A (AMERICAN CYANAMID CO) 11 March 1981 (1981-03-11) page 10, line 1 - line 10 claim 1 ---	1-7
X	WO 01 74363 A (NOVO NORDISK AS (DK)) 11 October 2001 (2001-10-11) the whole document ---	8-26
P,X	WO 02 28364 A (SIGMAPHARM INC) 11 April 2002 (2002-04-11) the whole document --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2002	05.07.02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Eva Johansson

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 638 310 A (SQUIBB BRISTOL MYERS CO) 15 February 1995 (1995-02-15) example 4 ---	1-26
A	WO 99 46245 A (HOECHST MARION ROUSSEL INC (US)) 16 September 1999 (1999-09-16) claim 66 ---	1-26
A	NÜRNBERG E ET AL: "Coating of cellulose products with colloidal silicon dioxide." DRUGS MADE IN GERMANY, vol. 39, no. 3, 1996, pages 104-107, XP002902513 the whole document ---	1-26
A	DATABASE STN INTERNATIONAL [Online] NÜRNBERG E ET AL: "Coating of cellulose products with highly dispersed silicic acid. Investigations on the improvement of tabletting properties demonstrated in low dose tablets." retrieved from HCA, accession no. 123:237711 XP002902514 abstract & PHARM. IND. , vol. 57, no. 3, 1995, pages 252-256, -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 02/00163

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9630016	A	03-10-1996	AU	5397496 A	16-10-1996
			CA	2215160 A1	03-10-1996
			WO	9630016 A2	03-10-1996
			EP	0817631 A2	14-01-1998
			HU	9900309 A2	28-05-1999
			IL	117670 A	29-02-2000
			JP	10511097 T	27-10-1998
			NO	974486 A	29-09-1997
			ZA	9602461 A	29-09-1997
GB 2055575	A	11-03-1981	AU	5957480 A	29-01-1981
			DE	3028082 A1	19-02-1981
			ES	493702 D0	01-08-1981
			ES	8106083 A1	01-10-1981
			FR	2462162 A1	13-02-1981
			IT	1128534 B	28-05-1986
			US	4442086 A	10-04-1984
			US	4578268 A	25-03-1986
WO 0174363	A	11-10-2001	AU	4409801 A	15-10-2001
			WO	0174363 A1	11-10-2001
			US	2001046990 A1	29-11-2001
WO 0228364	A	11-04-2002	WO	0228364 A2	11-04-2002
			WO	0228365 A2	11-04-2002
EP 0638310	A	15-02-1995	AU	6878294 A	09-02-1995
			CA	2129099 A1	03-02-1995
			CN	1118254 A	13-03-1996
			CZ	9401810 A3	15-02-1995
			EP	0638310 A1	15-02-1995
			FI	943569 A	03-02-1995
			HU	70951 A2	28-11-1995
			IL	110376 A	16-08-1998
			JP	7145052 A	06-06-1995
			NO	942854 A	03-02-1995
			NZ	264129 A	28-05-1996
			PL	304508 A1	06-02-1995
			US	5506248 A	09-04-1996
			ZA	9405672 A	06-03-1995
WO 9946245	A	16-09-1999	AU	2998899 A	27-09-1999
			BR	9909260 A	21-11-2000
			CA	2322501 A1	16-09-1999
			CN	1300280 T	20-06-2001
			EP	1192134 A2	03-04-2002
			JP	2002506059 T	26-02-2002
			NO	20004545 A	13-11-2000
			WO	9946245 A2	16-09-1999
			ZA	9901907 A	13-09-1999